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Monogenic Diabetes

"A Practical Overview for People with Diabetes and Health Professionals"

Although the most common forms of diabetes mellitus are type 1 and type 2 diabetes mellitus, there are other forms of diabetes, among which are monogenic diabetes, classically known as MODY (Maturity-Onset Diabetes of the Young). Confirming a correct diagnosis of monogenic diabetes can help personalize the patient's pharmacological treatment, their subsequent clinical follow-up, provide appropriate genetic counseling for their relatives, and facilitate a better understanding of the mechanisms related to hyperglycemia.

Unlike type 1 and type 2 diabetes mellitus (considered polygenic diseases where risk is influenced by genetic traits of many genes), in monogenic diabetes, hyperglycemia results from alterations affecting a single gene. Exceptionally rare forms of monogenic diabetes related to autoimmune processes, peripheral insulin action, and lipodystrophies have been described; however, this document will focus on monogenic diabetes that affects the proper functioning of the beta cell (the insulin-secreting cell in the pancreas), classically known as MODY (Maturity-Onset Diabetes of the Young).

Of note, as we will see later on, that there are different types of MODY diabetes, with differential clinical characteristics and treatment responses, and that the main limitation for diagnosing this type of diabetes is the lack of clinical suspicion or unfamiliarity on the part of the health care professional treating the person with diabetes.

WHAT IS THE FREQUENCY OF MONOGENIC DIABETES?

Although there are no studies conducted in the general population (with and without diabetes) that allow us to know with certainty the frequency of monogenic diabetes, the most recent studies conducted in Europe, the United States, and Australia estimate that approximately 0.5% of all people with diabetes (1 in 200) have some form of monogenic diabetes. This number is higher, reaching between 1% and 2%, when the studies refer to the pediatric population with diabetes (1 in 100 to 1 in 50 children with diabetes). Moreover, when genetic studies that confirm the diagnosis of monogenic diabetes are conducted in a clinical practice setting (not with a research objective) and following a series of clinical and laboratory criteria—such as diagnosis of diabetes before the age of 30, absence of autoimmunity against the beta cell, and persistence of insulin secretion several years after diagnosis—the percentage can increase to more than 20% of the people studied with diabetes (1 in 5)(1-4).

WHEN SHOULD WE SUSPECT THE POSSIBILITY OF MONOGENIC DIABETES?

As mentioned earlier, the main barrier to diagnosing patients with monogenic diabetes is the lack of clinical suspicion or unfamiliarity. Therefore, an appropriate description »

IT IS IMPORTANT TO EMPHASIZE THAT UP TO 6 MONTHS OF AGE, IT IS MORE COMMON FOR DIABETES TO BE DUE TO A MONOGENIC ALTERATION THAN TO AN AUTOIMMUNE ORIGIN

GEN (DISEASE)	% OF MODY	CLINICAL CHARACTERISTICS
GCK (MODY2)	30-50%	Stable mild hyperglycemia since birth. Low risk of complications. No need for treatment outside of pregnancy.
HNF1A (MODY3)	30-65%	Occasional transient neonatal hypoglycemia. Lowered threshold for glucosuria. Progressive defect in insulin secretion. Response to low doses of sulfonylureas. Response to GLP-1 analogs.
HNF4A (MODY1)	5-10%	Usual transient neonatal hypoglycemia. Progressive defect in insulin secretion. Response to sulfonylureas.
HNF1B (MODY5)	< 5%	Renal abnormalities. Some patients respond to sulfonylureas.
ABCC8 (MODY12)	< 1%	Neonatal diabetes. Response to sulfonylureas.
KCNJ11 (MODY13)	< 1%	Neonatal diabetes. Response to sulfonylureas.

TABLE 1. Frequency and Clinical Characteristics of Monogenic Diabetes.

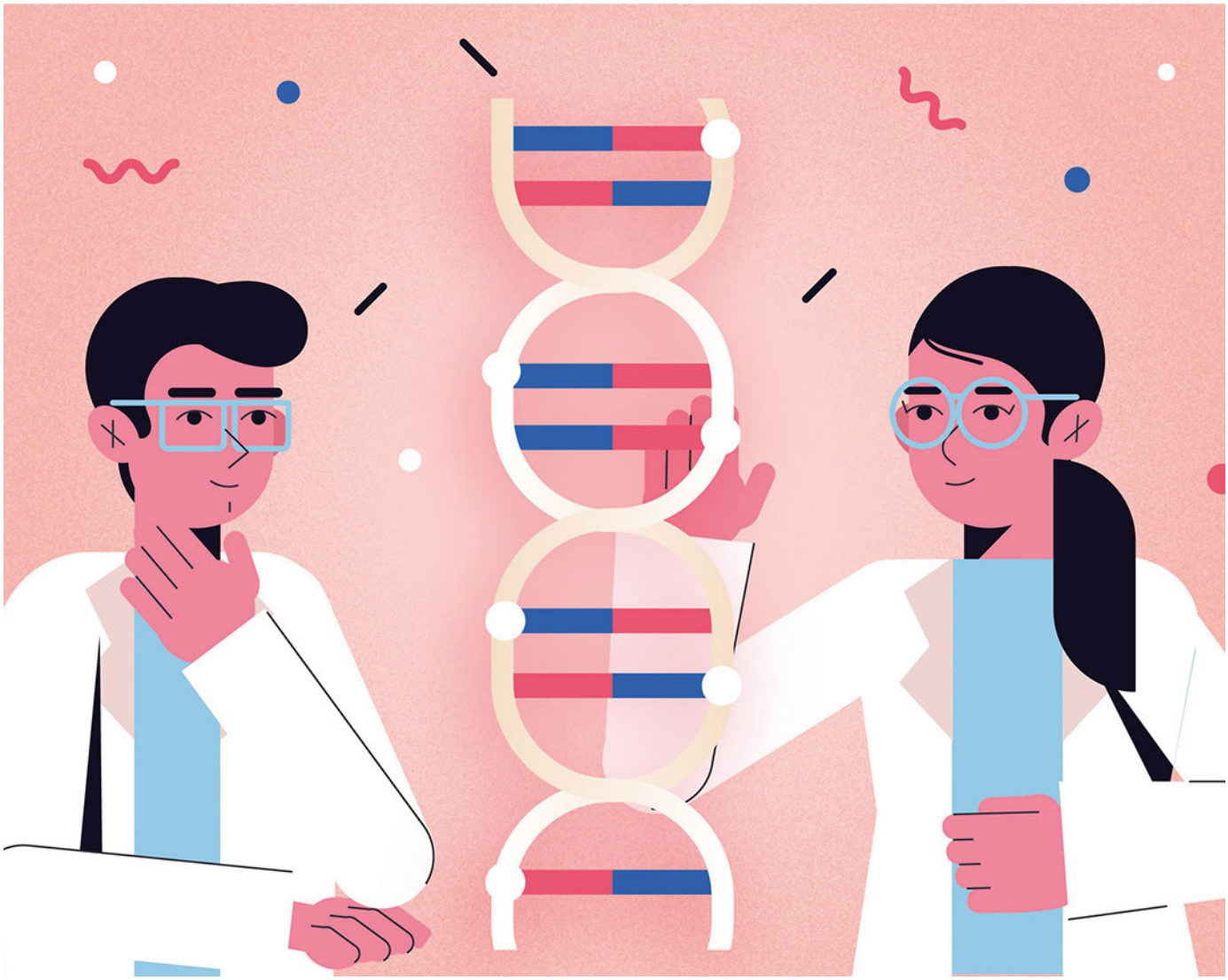
THE MAIN LIMITATION FOR ITS DIAGNOSIS IS THE LACK OF CLINICAL SUSPICION

» of the clinical characteristics of suspicion should be helpful.

Below, we describe 4 easily identifiable clinical profiles suggestive of monogenic diabetes:

Patients diagnosed with diabetes before 6 to 12 months of age. They are very rare but are clinically easy to recognize, and it is considered a clinical profile where genetic testing is mandatory. The term most widely used to describe the disease is "neonatal diabetes," as the patients were initially associated with diabetes onset within the first 30 to 50 days of life. Of note that up to 6 months of age, it is more common for diabetes to be due to a monogenic change than an autoimmune origin. Moreover, although this clinical profile develops in the pediatric age, it should be noted that some of these individuals could transition to adulthood without appropriate diagnosis or treatment (5-6).

Patients with diabetes associated with other extra-pancreatic conditions, such as deafness or renal cysts. Similar to the previous clinical scenario, these are very rare forms of diabetes, and in this case, the emergence of extra-pancreatic conditions should raise suspicion of the possibility of monogenic diabetes. In renal cysts and diabetes syndrome, it is essential to understand that renal signs (the most common being polycystic kidney disease) usually precede the diagnosis of diabetes and can even be detected in prenatal ultrasounds. Thus, these patients often undergo clinical follow-up in Nephrology Services, and the emergence of hyperglycemia should prompt consideration of their diagnosis and genetic testing. Other clinical signs described include epididymal cysts and uterine malformations. Additionally, the coexistence of diabetes and deafness should prompt suspicion of the syndrome known as MIDD (Maternally Inherited Deafness and Diabetes), which may be as- »



» sociated with changes to the mitochondrial DNA (a genetic material passed to offspring only by the mother, hence its maternal inheritance). Patients affected by this genetic alteration may also exhibit myopathy (muscle pain) or macular dystrophy (visual impairment) (5).

Patients with mild, stable hyperglycemia from birth. The presence of mild fasting hyperglycemia (100-125 mg/dL) that remains stable since birth could also be due to monogenic diabetes. In these cases, the most significant challenge in establishing clinical suspicion is that the asymptomatic nature of this condition can delay the diagnosis of diabetes (or hyperglycemia) until ages where it could be mistaken for type 2 diabetes mellitus. Furthermore, although it is a monogenic and hereditary disease, the absence of clinical symptoms and associated complications may lead the patient to be unaware of diabetes in their direct relatives. Given the mild, stable hyperglycemia from birth, observing normal glucose levels before assessment would allow us to rule out the diagnosis without the need for genetic testing (5-7).

Pediatric or young adult patients (younger than 30 years at the time of diagnosis) with atypical clinical features for type 1 or type 2 diabetes mellitus. In this case, it is crucial to include clinical or laboratory features that increase the likelihood of a positive result in the genetic study. Besides the age at diagnosis, two laboratory characteristics are typically evaluated. It is important to properly assess autoimmunity against the beta cell, including the most relevant antibody tests (anti-GAD, IA2, and ZnT8A). A positive result for beta cell autoimmunity would indicate a type 1 diabetes »

» diagnosis, even if the clinical presentation is not typical. The second significant laboratory marker to evaluate the possibility of monogenic diabetes is the C-peptide measurement, which helps assess insulin reserves in the beta cell. Low stimulated C-peptide levels (determined without fasting, after glucagon stimulation, or following a mixed-meal test) strongly suggest the presence of type 1 diabetes mellitus (5-7-9).

WHAT KIND OF TEST IS NEEDED TO CONFIRM THE DIAGNOSIS?

As previously mentioned, numerous genetic variants associated with monogenic diabetes due to beta cell dysfunction have been described; however, most are rare, and only 4 of them (GCK, HNF1A, HNF4A, HNF1B) account for more than 1% of all monogenic diabetes cases. Since it is a genetic disorder, confirmation of diagnosis will require demonstrating an alteration in the studied gene, for which a blood sample similar to those drawn for any standard laboratory test will suffice.

Different approaches to genetic testing can be considered, and their selection may depend on the clinical characteristics of the patient suspected of having monogenic diabetes.

Single-gene analysis. The presence of diabetes or mild, stable hyperglycemia since birth suggests mutations in GCK. Diabetes and maternally inherited deafness are associated, in most cases, with a point mutation in the mitochondrial gene MT-TL1, and in a few cases with point mutations in the mitochondrial genes MT-TE and MT-TK. Lastly, renal cysts and diabetes syndrome are related to mutations in HNF1B. These clinical alterations are not associated with other described genetic alterations, so isolated gene sequencing could be suitable in these cases.

Panel-based genetic testing. It allows simultaneous testing of a determined number of genes previously selected based on their relation to the studied clinical scenario. This type of genetic study will be particularly useful when the patient's clinical characteristics could be due to genetic alterations in different genes (e.g., HNF1A or HNF4A). However, of note that increasing the number of genes studied makes it more likely to detect genetic variants of uncertain significance, which may not always explain the clinical presentation observed in the patient.

WHAT RECOMMENDATIONS CAN BE GIVEN IF A PATIENT HAS MONOGENIC DIABETES?

As mentioned earlier, the primary endpoints of genetic confirmation are to offer individualized pharmacological treatment and follow-up for individuals with diabetes.

Monogenic diabetes associated with GCK mutations (MODY-2). Available evidence indicates that glycemic control does not show significant differences when these patients are on non-insulin anti-diabetic drugs or insulin, even after treatment withdrawal. Therefore, the general recommendation after genetic confirmation of monogenic diabetes associated with GCK mutations is to discontinue pharmacological treatment and reevaluate the patient. Regarding clinical follow-up, patients with monogenic diabetes associated with GCK mutations have a very low risk of hyperglycemia-related complications, so screening should be individualized. The most debated aspect of managing patients with monogenic diabetes associated with GCK mutations concerns the management of pregnant patients, where individualized treatment is required (5-7).

Monogenic diabetes associated with mutations in HNF1A (MODY-3) and HNF4A (MODY-1). It has been reported that patients with monogenic diabetes associated with mutations in HNF1A and HNF4A show an excellent response to treatment with sulfonylureas or glinides, and genetic confirmation would suggest attempting to change the treatment. Despite this, not all patients achieve adequate glycemic control with sulfonylureas. Regarding clinical follow-up associated with the risk of developing chronic complications, patients with monogenic diabetes associated with mutations in HNF1A and HNF4A present a risk equivalent to that observed in patients with other types of diabetes, so the recommendations for follow-up and control of comorbidities and cardiovascular risk factors should not differ from those applied to other patients with diabetes (5). »

THE PRIMAR ENDPOINTS OF GENETIC CONFIRMATION ARE TO OFFER THE PERSON WITH DIABETES AN INDIVIDUALIZED PHARMACOLOGICAL TREATMENT AND FOLLOW-UP

» ***Patients with monogenic diabetes associated with mutations in HNF1B (MODY-5).*** These patients may be sensitive to treatment with sulfonylureas, although in no case will the results be as expected for patients with MODY-3. Thus, treatment with sulfonylureas could be a therapeutic option, but afterward, the treatment will need to be adjusted to the individual patient's response (10).

Patients with monogenic diabetes associated with mutations in KCNJ11 and ABCC8. This is a clinical profile that develops in childhood, and it has been shown that these patients respond well to treatment with sulfonylureas, making this the preferred therapeutic option (6).

Other patients with monogenic diabetes (associated with APPL1, BLK, CEL, INS, KLF11, NEUROD1, PAX4, and PDX1). Due to their low prevalence, there are no specific recommendations regarding their pharmacological treatment or clinical follow-up.

Summary:

As conclusions, we cannot forget that there are other types of diabetes beyond type 1 and type 2 diabetes mellitus, and that a correct diagnosis of monogenic diabetes can allow us to withdraw pharmacological treatment and space out screening tests for chronic complications, as is the case with diabetes associated with mutations in GCK, or it may allow us to discontinue insulin treatment while achieving better glycemic control with oral pharmacological therapy, as occurs in diabetes associated with mutations in HNF1A. D

REFERENCES:

1. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, et al. Prevalence, characteristics and clinical diagnosis of Maturity Onset Diabetes of the Young due to mutations in HNF1A, HNF4A, and Glucokinase: results from the SEARCH for diabetes in Youth. J Clin Endocrinol Metab. 2013; 98: 4055-62.
2. Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, et al. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the UK pediatric diabetes population with monogenic diabetes. Diabetes Care. 2016; 39: 1879-88.
3. Rudland VL, Hinchcliffe M, Pinner J, Cole S, Mercorella B, Molyneaux L, et al. Identifying glucokinase monogenic diabetes in a multiethnic gestational diabetes mellitus cohort: new pregnancy screening criteria and utility of HbA1c. Diabetes Care. 2016; 39: 50-52.
4. Shields BM, Shepherd M, Hudson M, McDonald TJ, Colclough K, Peters J, et al. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in Young-onset patients. Diabetes Care. 2017; 40: 1017–25.
5. Murphy R1, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab. 2008; 4: 200-13.
6. Lemelman MB, Letourneau L, Greeley SAW. Neonatal Diabetes Mellitus: An Update on Diagnosis and Management. Clin Perinatol. 2018; 45: 41-59.
7. Pinés Corrales PJ, López Garrido MP, Louhibi Rubio L, Aznar Rodríguez S, López Jiménez LM, Lamas Oliveira C, et al. Importance of clinical variables in the diagnosis of MODY2 and MODY3. Endocrinol Nutr. 2011; 58: 341-6.
8. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. JAMA. 2014; 311: 279-286.
9. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med. 2013; 30: 803-17.
10. Carrillo E, Lomas A, Pinés PJ, Lamas C. Long-lasting response to oral therapy in a young male with monogenic diabetes as part of HNF1B-related disease. Endocrinol Diabetes Metab Case Rep. 2017. pii: 17-0052.